New drug classes

The camptothecins

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Supported by detailed understanding of their mechanism of action, and facilitated by chemical manipulations that have amplified their solubility, the camptothecins have advanced to the forefront of several areas of therapeutic and developmental chemotherapy. Additive and synergistic laboratory interactions with other cytotoxic drugs have been exploited to allow development of camptothecin-based multidrug regimens, which are showing important activity in several malignancies. Topotecan and irinotecan are already in widespread use in clinical practice, and newer agents with promising preclinical activity are in various stages of clinical assessment. As knowledge of molecular and biochemical mechanisms of action and resistance continues to expand, newer and better camptothecin-based strategies for treatment of malignant disease are likely to evolve.

Camptothecin is a plant alkaloid present in wood, bark, and fruit of the Asian tree *Camptotheca acuminata*. From a shaky beginning complicated by toxic effects and logistical issues, camptothecin derivatives have advanced to become standard components in the treatment of several malignancies. Here, we review progress to date with established drugs in this class, and we discuss some new analogues in clinical development.

History of camptothecin

The US National Cancer Institute screening programme identified camptothecin as a drug with potential antitumour activity in 1966.[1] Promising preclinical results were seen in mouse L1210 leukaemia and rat Walker carcinosarcoma models. However, the drug was poorly soluble, a problem that greatly hampered its initial clinical development.

Preclinical data showing camptothecin activity in tumours of both colonic and gastric origin, and toxic effects of the drug to the digestive tract, led to phase 1 trials focusing largely on gastrointestinal malignancies. In these initial trials, myelosuppression was identified as the primary dose-limiting toxic effect. Haemorrhagic cystitis also developed unpredictably in a few patients, and was occasionally severe. In retrospect, haemorrhagic cystitis can most probably be explained by the in-vivo chemistry of camptothecin.

Camptothecin has a five-ring structure (figure). Early assessments identified the importance of the 20*S* chiral carbon for activity, and also noted a dynamic equilibrium between the closed ring lactone and open-ring carboxylic acid forms (figure). The closed ring lactone has most cytotoxic activity. At neutral and alkaline pH, equilibrium favours the essentially inactive carboxy-acid form.

However, the importance of the intact lactone ring on activity was not fully appreciated initially. To deal with insolubility of the parent compound, the sodium salt of camptothecin was studied. This resulted in irreversible opening of the lactone ring, so that very high concentrations of the drug were required for clinical activity. This outcome could have contributed to the unpredictable nature of the toxic effects initially seen, since equilibrium between the carboxylic acid and lactone forms is largely dictated by ambient pH. For example, acidity of the bladder would favour dissociation of the sodium salt. These conditions also facilitate spontaneous closure of the lactone ring, thus potentially producing large amounts of active drug in the urine. Variability of the collecting system might have further contributed to unpredictability of haemorrhagic cystitis. Despite great toxic effects, some activity was seen, leading to phase 2 trials.

In 1972, workers on a phase 2 study looked at efficacy and safety in 61 patients with adenocarcinoma of gastrointestinal origin.[2] Again, haematological toxic effects seemed to be dose-limiting. With only three of 61 patients obtaining an objective response, and toxic effects being severe and unpredictable, further development of camptothecins was abandoned. Not until the mechanism of action of camptothecin was identified was interest in these drugs—and in development of more water-soluble analogues—rekindled (panel).

Topoisomerase 1

Although discovered in the 1970s, the role of topoisomerase 1 as an important enzyme in DNA replication was not fully appreciated until the 1980s. DNA normally exists as a supercoiled double helix. During replication, it unwinds, with single strands serving as a template for synthesis of new strands. To relieve the torsional stress that develops ahead of the replication fork, transient cleavage of one or both strands of DNA is needed. Topoisomerases facilitate this process. Topoisomerase 2 causes transient double-stranded

Search strategy and selection criteria

Data for this review were identified by searches of MEDLINE and PubMed (restricted to English language reports) and references from relevant articles, with the search terms topotecan, irinotecan, 9-amino-camptothecin, 9-nitrocamptothecin, exatecan, PEG camptothecin, and glycoconjugate camptothecin. Abstracts were included only if they related directly to drugs and included results.

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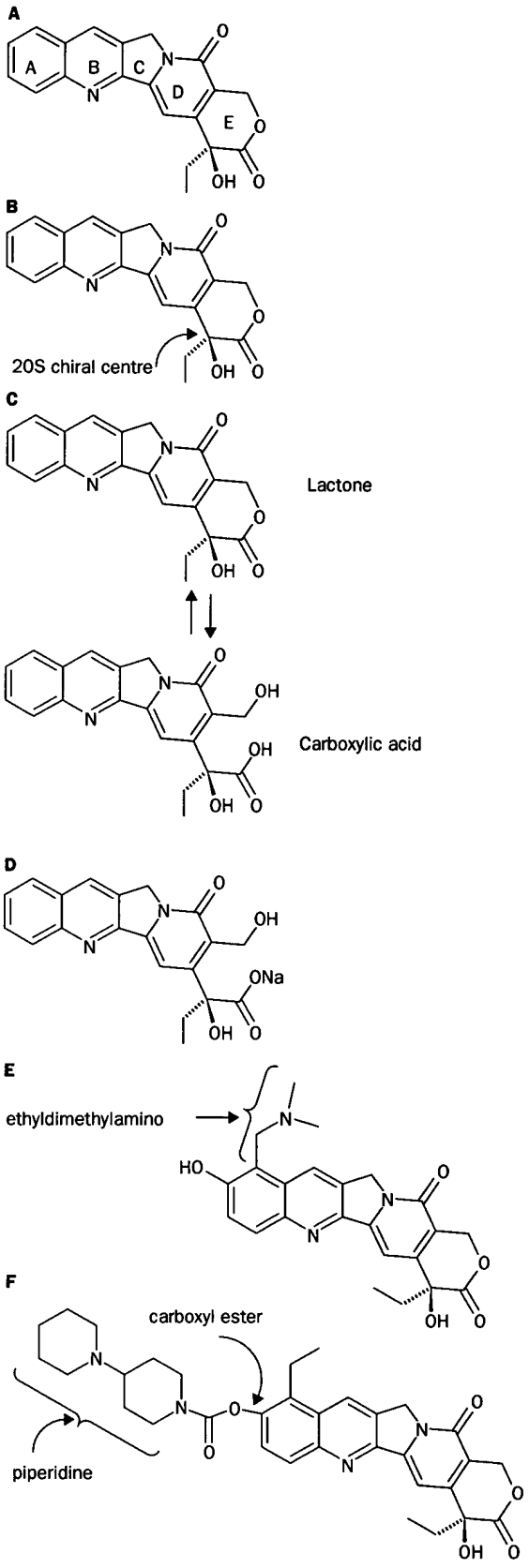

Structures of camptothecin class of drugs
(A) Camptothecin. (B) 20S chiral centre. (C) Dynamic equilibrium of camptothecin. (D) Camptothecin sodium salt. (E) Topotecan. (F) Irinotecan.

breaks, whereas topoisomerase 1 causes single-strand breaks. This action allows for rotation of the broken strand around the intact strand. Topoisomerase 1 then re-ligates the broken strand to restore integrity of double-stranded DNA.

In 1985, topoisomerase 1 was found to be the target of camptothecin.[3,4] The drug reversibly induces single-strand breaks, thereby affecting the cell's capacity to replicate. Camptothecin stabilises the so-called cleavable complex between topoisomerase 1 and DNA. These stabilised breaks are fully reversible and non-lethal.[5] However, when a DNA replication fork collides with the cleavable complex, single-strand breaks are converted to irreversible double-strand breaks.[3,6] Apoptotic cell death is then mediated by caspase activation. Inhibition of caspase activation shifts the cells from apoptosis to transient G1 arrest followed by cell necrosis.[7] Thus, the mechanisms of cell death need active DNA replication to be happening, resulting in cytotoxic effects from camptothecin that is S-phase-specific. Indeed, cells in S-phase in vitro have been shown to be 100–1000 times more sensitive to camptothecin than cells in G1 or G2.[8]

Results of early experiments showed camptothecin sensitivity in cancer cell lines was directly correlated to topoisomerase 1 concentrations.[9] Other investigators reported topoisomerase 1 to be overexpressed in tumour tissue of patients with adenocarcinoma of the colon.[10] Further investigation noted amplified concentrations of the enzyme in other tumours.[11] Identification of topoisomerase 1 as a viable target for antineoplastic treatment, and elucidation of its inhibition as the mechanism of action of camptothecin, led to renewed efforts to develop soluble analogues of camptothecin.

Topotecan

Topotecan (9-[(dimethylamino)methyl]-10-hydroxy-camptothecin) was the first camptothecin analogue to be approved for clinical use by the US Food and Drug Administration (FDA). It is water-soluble because of its side-chain at carbon 9 of the A ring (figure). Results of preclinical studies suggested topotecan to have excellent antitumour activity in vitro.[12] Tumour xenograft models showed activity in many tumour types, including adenocarcinomas of the ovary and colon, tumours of the central nervous system, and sarcomas.[13–15] Workers on initial phase 1 trials assessed treatment with topotecan as a daily 30 min infusion for 5 consecutive days repeated every 3 or 4 weeks.[16,17] In each of these studies, the dose-limiting toxic effect was myelosuppression. In other phase 1 trials, continuous or protracted infusions were assessed.[18,19] Although phase 1 studies seemed to suggest a higher response rate with extended infusions or frequent dosing, phase 2 studies in unresectable and metastatic non-small-cell lung cancer and in advanced breast cancer did not confirm this apparent advantage.[20,21]

Early phase 2 studies mainly focused on colorectal and gastric cancer; however very little evidence of activity was seen, and toxic effects were considerable.[22–24] Indications of activity in ovarian and small-cell lung cancer in phase 1 trials led to further investigation of topotecan in these areas. An oral formulation of topotecan also continues to be studied.

Ovarian cancer

The pivotal study in the 1996 FDA approval of topotecan for relapsed ovarian cancer was a randomised phase 3 trial by ten Bokkel Huinink and colleagues.[25] These workers assessed topotecan versus paclitaxel in patients with recurrent ovarian cancer after a platinum-containing

Drug	Manufacturer	Current status
Irinotecan (Camptosar, CPT-11)	Pharmacia	Approved
Topotecan (Hycamptin)	GlaxoSmithKline	Approved
BAY 38-3441	Bayer AG	Phase 3
9-nitrocamptothecin (Orethecin, formally rubitecan)	SuperGen	Phase 2/3
Exatecan (DX-8951)	Daiichi Pharmaceutical	Phase 2/3
9-aminocamptothecin	None	Phase 2

regimen or who had not responded to a regimen containing platinum. Topotecan was administered at 1·5 mg/m² daily for 5 days, repeated every 21 days. No significant survival benefit was recorded; however, topotecan did have a significant benefit over paclitaxel in time to progression (23 *vs* 14 weeks, p=0·002).

Although topotecan-induced myelosuppression is short-lived and non-cumulative, this drug can be a challenge to administer to any pretreated population. The drug is largely cleared by renal excretion of the carboxylate form. Topotecan-induced myelosuppression rises with reduced renal clearance, which might be related to platinum pretreatment or disease. When neutropenia is the only toxic effect, colony-stimulating factors are preferred to dose reduction of topotecan. Because reduced renal clearance amplifies the myelotoxic effects of topotecan, carboplatin has been postulated as a reasonable substitute for cisplatin. In a phase 1 study of topotecan and carboplatin, two dose schedules of topotecan were assessed: days 1 through 5 and days 8 through 12.[26] Substantial treatment delays in 36% and 53% of patients, respectively, were the result of significant myelosuppression. A randomised trial in patients with recurrent or persistent platinum and paclitaxel-resistant ovarian or primary peritoneal cancer is underway comparing carboplatin plus paclitaxel with four other combinations, one of which is topotecan plus carboplatin.[27]

Oral topotecan offers a more convenient route of administration. Results of a phase 1 study investigating the schedule of oral topotecan for 5 consecutive days every 21 days in 29 patients with solid tumours showed the maximally tolerated daily dose to be 2·3 mg/m², and the dose-limiting toxic effect to be granulocytopenia.[28] This result led to a phase 2 study of this schedule in 116 patients needing second-line chemotherapy for advanced ovarian cancer.[29] The response rate was 22% with similar grade 4 toxic effects to those seen with intravenous topotecan. In a randomised trial of oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer,[30] topotecan was again given for 5 consecutive days every 21 days with daily oral and intravenous doses of 2·3 or 1·5 mg/m², respectively. The difference in response rates was not significant (14% and 20%, respectively). Grade 4 neutropenia was more common in patients receiving intravenous (51% *vs* 15%) but intravenous topotecan did carry a small survival advantage (58 *vs* 51 weeks, p=0·033).

Small-cell lung cancer

A phase 3 Eastern Cooperative Oncology Group (ECOG) trial studied the efficacy of topotecan as a single agent in patients with extensive stage small-cell lung cancer,[31] on the basis of results of two small phase 2 trials showing single-agent response rates of about 37%.[32,33] Patients who had either a response or stable disease after four cycles of cisplatin and etoposide were randomly allocated to topotecan alone for four cycles or observation. Although progression-free survival was improved, no overall survival benefit was seen. A randomised phase 2 study revealed no difference in response rates between oral and the intravenous groups (23 *vs* 15%, respectively) and no difference in survival was recorded.[34] Many other studies are underway comparing oral and intravenous forms of topotecan.

Status of topotecan

Topotecan has gained broad acceptance in clinical use in these refractory malignancies. Clinicians use this drug routinely, and thus clearly feel that it is beneficial to their patients; however, no randomised trial has shown a survival advantage with topotecan.

Irinotecan

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin) was the first water-soluble semisynthetic derivative of camptothecin to enter clinical trials. After initial development in Japan, the drug has been licensed to several different pharmaceutical firms and has undergone a truly global development plan. Investigation began in the late 1980s, with phase 1 studies in Japan assessing a bolus infusion every week and a 5-day continuous infusion.[35,36] Irinotecan became commercially available in Japan in 1994, where its approved indications were cancers of the lung (small-cell and non-small-cell), cervix, and ovaries. Irinotecan was approved in Europe in 1995 as a second-line agent for colon cancer, 1 year before European approval of topotecan. Irinotecan was approved in the USA in 1996 for treatment of advanced colorectal cancer refractory to fluorouracil.

Metabolism and pharmacokinetics

A unique characteristic of irinotecan is its bulky dipiperidino side-chain linked to the camptothecin molecule via a carboxyl-ester bond (figure). This side-chain, although providing necessary solubility, leads to a substantial reduction in anticancer activity. Cleavage of the side-chain by carboxylesterases—found mainly in the liver and gastrointestinal tract—forms the metabolite SN-38 (7-ethyl-10-hydroxycamptothecin). SN-38 is as much as 1000-fold more potent in inhibition of topoisomerase 1 than irinotecan and is thus the predominant active form of the drug.[37] Irinotecan has been said to be essentially a prodrug for SN-38, but this analysis might be overly simplistic. Although SN-38 has 2–3 logs greater activity than irinotecan, irinotecan concentrations might be 2–3 logs higher than those of SN-38. Thus, the relative contribution of irinotecan, may not be insignificant.

Clearance of SN-38 is by uridine diphosphate glycosyltransferase 1 family polypeptide A1 (UGT1A1), an enzyme important for biliary glucuronidation. Although most tissues can activate irinotecan into SN-38 by carboxylesterases, only the liver can detoxify SN-38 by glucuronidation. Inhibition of UGT1A1 increases SN-38 concentrations.[38,39] Furthermore, patients with reduced activity of this enzyme (Gilbert's disease) have greatly amplified toxic effects to irinotecan.[40] Results of a prospective pharmacogenetic study showed that patients with a (TA)₇TAA polymorphism in the promoter region of the UGT1A1 gene are at high risk for serious diarrhoea and neutropenia, especially those with a homozygous mutation.[41] Administration of irinotecan in any patient with raised bilirubin concentrations or significant hepatic

dysfunction is not recommended, since evidence-based guidelines have not been published. Patients with renal insufficiency do not seem to need dose modification.

Peak plasma concentrations of irinotecan arise soon after infusion. The peak concentration of SN-38 is more variable, with times ranging from 30 to 90 min after infusion.[42] Although irinotecan has a short half-life, SN-38's half-life is about 11·5 h.[43,44] Preclinical data in multiple human tumour xenograft models have suggested that repeated intermittent treatment scheduling might be superior to single injections of the same total drug doses.[45] Phase 1 studies have assessed many schedules, including every 3 weeks, every week for 4 weeks, or for 3 consecutive days every 3 weeks.[43,44,46]

Toxic effects and management of side-effects

Although the initial dose-limiting toxic effect of irinotecan given every 3 weeks was myelosuppression, the main effect with the other schedules was diarrhoea. Extended continuous intravenous infusion has also been investigated. Because conversion of irinotecan to SN-38 during prolonged infusion is thought to be more effective, irinotecan administration was studied as a 5-day continuous infusion.[35] The dose-limiting toxic effect was dose-dependent diarrhoea. Diarrhoea was correlated to irinotecan concentrations and not to amount of SN-38, whereas myelosuppression was correlated to SN-38 concentrations and not to amount of irinotecan. No correlation was seen between the AUC (area under the curve) of irinotecan and SN-38.

Diarrhoea and myelosuppression are the most typical and significant toxic effects of irinotecan. The diarrhoea can happen early, during or within a few hours of infusion, or be delayed beyond 24 h post infusion, with incidence of grade 3 or higher diarrhoea ranging from 22% to 29%.[47-49] Early-onset diarrhoea is a cholinergic effect, often accompanied by cramping, flushing, and sweating. Anticholinergic drugs such as atropine seem to easily reverse this side-effect. Diarrhoea that is not early-onset is treated with loperamide, and identification of high-dose loperamide as an effective remedy for this toxic effect greatly facilitated development of irinotecan.[50] Late-onset diarrhoea seems to be a primary secretory diarrhoea, although components of exudative diarrhoea may also be.[51] Racecadotril (acetorphan), an antisecretory drug that has been used to treat diarrhoea, has been studied too.[52] Loperamide in combination with racecadotril may have advantages over loperamide alone,[51] but larger randomised studies will be needed to establish a role for racecadotril in the management of irinotecan-induced toxic effects.

COX-2 (cyclo-oxygenase 2) inhibitors reduce thromboxane A2, a molecule that contributes to diarrhoea by stimulation of chloride ion secretion. However, concentrations of prostaglandin E2 are normal in patients with irinotecan-associated diarrhoea,[51] and early clinical experience does not suggest that COX-2 inhibitors have any effect on this complication.[53]

Neomycin given orally reduces amount of β-glucuronidases produced by microflora in the large bowel. These enzymes catalyse hydrolysis of SN-38G to active SN-38, which is thought to control delayed-type diarrhoea. Results of a small trial suggested a reduction in faecal concentrations of SN-38 after administration of neomycin 1000 mg three times a day on days −2 through 5 and irinotecan 350 mg/m² given every 3 weeks.[54] Systemic concentrations of SN-38 were not affected. Adequately powered randomised trials are needed to verify these findings.

Colorectal cancer

Irinotecan's largest use today is in treatment of advanced colorectal cancer. On initial phase 1 trials of this drug, activity was noted in some patients with colorectal cancer refractory to treatment, leading to an early trial in patients with fluorouracil-refractory disease.[55] Results of an early phase 2 trial in chemotherapy-naive patients showed a major objective response rate of 32%.[47] Response rates of 13% in a pooled analysis of 304 patients with fluorouracil-refractory colorectal cancer led to accelerated approval by the FDA in June, 1996. Results of two confirmatory phase 3 studies—one with 350 mg/m² of irinotecan every 3 weeks versus best supportive care and the other comparing 300–350 mg/m² of irinotecan with infusional fluorouracil—showed survival advantages for the irinotecan arms. Results of these trials led to full final FDA approval of the drug for second-line treatment of colorectal cancer in 1998.[48,49]

The success of irinotecan in fluorouracil-refractory patients led to efforts to combine these drugs into effective first-line regimens.[56,57] Workers on a large randomised study of 683 patients compared a combination of irinotecan every week plus bolus fluorouracil and folinic acid with fluorouracil and folinic acid alone. For regulatory reasons, an irinotecan-alone arm was also included.[58] The primary objective—progression-free survival—showed the irinotecan plus fluorouracil and folinic acid arm was superior to fluorouracil and folinic acid alone (median 7·0 months *vs* 4·3 months; p=0·004). The response rate for the combination was nearly double in the irinotecan plus fluorouracil and folinic acid arm, and median overall survival proved superior to fluorouracil and folinic acid alone (14·8 months *vs* 12·6 months; p=0·04). As anticipated, irinotecan alone was similar in efficacy to fluorouracil and folinic acid alone.

In a parallel trial in Europe, irinotecan in combination chemotherapy was tested by Douillard and colleagues.[59] In this phase 3 study, 387 patients with previously untreated metastatic colorectal cancer were assigned one of two infusional fluorouracil and folinic acid regimens, and were then randomised to this regimen with or without irinotecan. Again, a significant improved response rate (49 *vs* 31%), time to progression (6·7 *vs* 4·4 months) and overall survival (17·4 *vs* 14·1 months) was seen in the irinotecan plus fluorouracil and folinic acid arm versus the fluorouracil and folinic acid alone arm. Based on the results of these studies, irinotecan subsequently gained approval as a first-line drug in combination with fluorouracil and folinic acid for treatment of colorectal cancer in the metastatic setting.

Upper gastrointestinal malignancies

Results of a phase 2 study showed single-agent irinotecan to be active in gastric cancer, with a response rate of 17%.[60] Although the modest activity of this drug is of limited use in upper gastrointestinal malignancies, the combination of irinotecan with cisplatin has become of great interest. In vitro, cisplatin and irinotecan have shown striking sequence-dependent synergy in various cancer cell lines. Peak synergy seems to be achieved when cisplatin is given immediately before or in combination with SN-38.[61,62] Several potential mechanisms of synergy exist between cisplatin and irinotecan. Cisplatin causes platinum-DNA adducts (intrastrand cross-links) and DNA cross-links (interstrand cross-links). DNA adducts must be removed by excision-repair. This process requires unscheduled DNA synthesis, which in turn needs uncoiling of DNA, which is facilitated by topoisomerase 1. Inhibitors of this

enzyme, by interfering with DNA unwinding, might potentiate platinum-DNA adducts and so contribute to their cytotoxic effects. Furthermore, cisplatin might also amplify SN-38 inhibition of topoisomerase 1.[63]

Saltz and colleagues[64] investigated—in a phase 1 study—administration of cisplatin every week immediately followed by irinotecan, giving both drugs as a 4 weeks on 2 weeks off schedule in patients with advanced solid tumours. The regimen was noted to be well tolerated, with evidence of great antitumour activity. This regimen was then studied in a formal phase 2 study in patients with oesophageal cancer.[65] A major objective response rate of over 50% was recorded, with manageable toxic effects. These promising results prompted a phase 1 trial of irinotecan, cisplatin, and concurrent radiotherapy every week in patients with locally advanced oesophageal cancer.[66] Phase 2 trials are in progress.

With a somewhat different administration schedule, Boku and co-workers[67] also reported their phase 2 results in patients with metastatic gastric cancer with the combination of cisplatin and irinotecan. Irinotecan was given on days 1 and 15, cisplatin on day 1 only. The reported response rate was 48%.

Results of a phase 2 trial investigating single-agent irinotecan in patients with pancreatic cancer has also shown some modest activity.[68] Workers on this study used 350 mg/m² of irinotecan every 3 weeks and induced a partial response in three (9%) of 32 assessable patients. Overall median survival time in this study was 5·2 months (range 0·4 to 22+ months). This modest activity led to phase 2 studies in combination with gemcitabine. Rocha Lima and colleagues studied 45 patients in a phase 2 trial of gemcitabine 1000 mg/m² over 30 min, followed by irinotecan 100 mg/m² over 90 min on days 1 and 8, repeated every 3 weeks.[69] A response rate of 20% was seen. A phase 3 study of irinotecan with gemcitabine versus gemcitabine alone is underway.

Non-small-cell lung cancer

Although single-agent irinotecan has had disappointing results in patients with lung cancer, combination treatment with cisplatin has shown promising response rates. Date and colleagues[70] did a phase 1 and 2 study looking at the combination of cisplatin and irinotecan in people with non-small-cell lung cancer. The results showed an initial response rate of 73% with a dose schedule of cisplatin 60 mg/m² plus irinotecan 50 mg/m² as neoadjuvant chemotherapy in N2 disease. Two phase 3 studies have investigated combination treatment. Masuda and co-workers[71] did a three-arm prospective randomised trial of cisplatin in combination with vindesine versus cisplatin in combination with irinotecan versus irinotecan alone in people with non-small-cell lung cancer. No significant differences were reported in response rates or survival between the three arms. Niho and colleagues[72] also did a phase 3 trial comparing cisplatin plus either vindesine or irinotecan. Again, no survival differences were noted.

Small-cell lung cancer

High response rates with combination cisplatin and irinotecan have been reported in people with small-cell lung cancer. In a phase 3 trial, chemotherapy-naive patients with extensive small-cell lung cancer were randomly allocated either cisplatin plus irinotecan or cisplatin plus etoposide.[73] The irinotecan group received the drug every week for 3 weeks at 60 mg/m², with cisplatin 60 mg/m² being given on day 1. This schedule was repeated every 4 weeks for a total of four cycles. The etoposide group received the drug at 100 mg/m² on days 1, 2, and 3 and cisplatin 80 mg/m² on day 1, repeated every 3 weeks for four cycles This trial was stopped early because of a substantial 2-year survival difference of 19·5 *vs* 5·2%, and a difference in median survival (12·8 *vs* 9·4 months, p=0·002), for the irinotecan and etoposide regimens, respectively.

Other tumours

Irinotecan continues to be studied in other cancers such as mesothelioma, ovarian cancer, and head and neck cancer in which previous cisplatin-containing regimens have shown activity. Furthermore, preliminary data from a phase 2 study have shown irinotecan to be a promising agent in patients with refractory metastatic breast cancer.[74] Irinotecan has also shown activity in refractory non-Hodgkin lymphomas. Further studies will focus on single-agent and combination irinotecan in various malignant diseases.

9-aminocamptothecin

9-aminocamptothecin was shown in early studies to have very impressive preclinical activity. Preclinical data in colorectal xenografts in mice were among the most promising seen in this disease.[10] This drug did not have the solubility of topotecan or irinotecan, and formulation was a great challenge. Initially, an intravenous preparation in a Cremophor carrier was developed for clinical use. However, phase 2 trials in colorectal cancer failed to show any significant activity despite substantial myelosuppression.[75–77] Similar disappointing results were reported in non-small-cell lung cancer.[78] A colloidal dispersion formulation was also disappointing.[79] Further development therefore does not seem to be justified, and studies are not planned.

9-nitrocamptothecin

9-nitrocamptothecin is another water-insoluble analogue that is being developed in an oral formulation. Results of an early phase 2 study looking at activity in ovarian or primary peritoneal cancer did show some modest activity; however, toxic effects similar to its parent compound (haematological toxic effects and haemorrhagic cystitis) were substantial.[80] Workers on other phase 2 studies have examined 9-nitrocamptothecin activity in glioblastoma multiforme and melanoma, confirming many of its toxic effects without clinical benefit.[81,82] In a phase 2 trial of the drug, treatment as a single agent was assessed in 60 patients with advanced pancreatic cancer.[83] 9-nitrocamptothecin was administered at 1·5 mg/m² daily for 5 days every week. With conventional two-dimensional (50% reduction in cross-sectional area) criteria for partial response and assessment of all patients who initiated treatment, a response rate of 8% was seen. Although toxic effects seemed to be substantial, this drug is being assessed in many phase 3 trials in patients with pancreatic cancer.

Exatecan

Exatecan is a water-soluble camptothecin analogue that was designed to be more potent than other analogues. Many phase 1 schedules were investigated, including a 30 min infusion five times a day every 21 days, a 24 h infusion given every 21 days, a 30 min infusion given every 21 days, and a 24 h infusion given every week.[84,85] Results of phase 1 studies showed the drug to be well tolerated, with predictable myelosuppression as the dose-limiting toxic effect. Examination of exatecan activity in a phase 2 trial saw no activity in colorectal-cancer patients.[86]

Three studies have investigated activity of exatecan in biliary and pancreatic cancer.[87-89] Modest activity was seen. In a phase 1 trial looking at exatecan in combination with gemcitabine, the phase 2 and 3 doses for this combination were identified.[90] A phase 3 trial of this combination versus gemcitabine alone is underway. Further large randomised studies could investigate exatecan in combination.

Camptothecin glycoconjugates

Activity of the camptothecin class of compounds is derived from the closed lactone E ring. Research into equilibrium of the active lactone form and the inactive carboxylate form has shown a shift towards the inactive form with binding to albumin. Polyethyleneglycol conjugates enhance lactone-ring stability and water solubility of the camptothecins. In 1999, conjugated 9-amino-camptothecin entered a phase 1 trial.[91] The dose-limiting toxic effect was again myelosuppression. Whether this formulation will affect this drug's activity is unclear. Presently, a glycoconjugated compound, BAY 38-3441, seems to have strong in-vitro activity. Two phase 1 studies have been done with this compound given once every 3 weeks and daily for 5 days every 3 weeks.[92,93] The dose-limiting toxic effects seem to be renal problems and myelosuppression, respectively. Further phase 2 and phase 3 development is planned.

Conflict of interest statement

L B Saltz receives research funding from Pharmacia and Bayer Oncology.

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